

Review Article

Congenital tuberculosis: a review article

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ABSTRACT

TB remains a leading cause of morbidity and mortality in developing countries. The incidence of congenital TB is underestimated. Current recommendations regarding the management of neonates of mothers with tuberculosis are variable and no tangible guidelines have been advised. Congenital TB is fatal if untreated, moreover the mortality and morbidity is increased if the diagnosis and treatment is delayed. Therefore, the treating clinician should be aware of the unusual presentation of congenital TB. A high suspicion and good screening of mothers and neonates is of paramount importance. Congenital tuberculosis is diagnosed by Cantwell criteria. Isoniazid prophylaxis for 6 months is recommended in neonates born to mothers with TB who are infectious. Breastfeeding should be continued, and isolation is recommended only in certain circumstances such as mother is infectious, has multidrug resistant tuberculosis or non-adherent to treatment. BCG vaccine is recommended in all neonates however, the timing of administration varies according to various guidelines. Neonate diagnosed with congenital TB should be treated with anti-tubercular drug regimen.

Keywords: Congenital tuberculosis, Paediatric tuberculosis guidelines

INTRODUCTION

Tuberculosis (TB) is a chronic disease caused by the bacillus *Mycobacterium tuberculosis* and it spreads through droplets. TB is a global public health problem and WHO recognizes it as one of the top 10 causes of death worldwide.¹

Although the incidence has decreased in the developed countries after the introduction of the multidrug treatment (DOTS), developing nations are still struggling with this debilitating disease.

Transmission of disease is well known via transplacental transmission through the umbilical vein to the fetus, or through the ingestion of infected amniotic fluid. Although vertical transmission is rare, neonatal mortality and

morbidity is very high. Early diagnosis of congenital TB is challenging because of its non-specific presentation; however, it should be distinguished from the more frequent acquired neonatal TB, in which the infant is infected after birth by a person suffering from the disease. It is extremely important to diagnose the disease early in the course and start treatment regimen for enhanced outcomes.

DEFINITION

Congenital tuberculosis is infection acquired to a newborn from infected mother during the intrauterine period or during normal birth. Only 300 cases were reported in the scientific literature till 1989; subsequently, 58 cases in 1994 and, from 2001 to December 2005, 18 more cases have been mentioned.² Only about 10 cases have been reported in India.

TRANSMISSION

Tuberculosis is relatively common during pregnancy as pregnancy is a state of physiological immunosuppression, additionally there has been an increase in the incidence of HIV. However, congenital TB is rare because tuberculosis primarily causes infertility.³ Moreover, placenta acts as a physical barrier for the bacilli.

Congenital TB is transmitted vertically when the maternal mycobacterium bacilli is transmitted hematogenously through the umbilical vein to the fetus or through the ingestion or inhalation of infected amniotic fluid in utero or during delivery.

After crossing the placenta through the umbilical vein, a primary focus develops in the fetal liver with involvement of the periportal lymph nodes and secondarily the lungs are infected. If the infection occurs because of ingestion or inhalation of infected amniotic fluid, fetal lungs and gut are primarily infected.

The bacilli remain inactive in the fetal lung during the fetal period. After birth when there is an increase in the oxygenation and pulmonary perfusion, the bacilli may become active and causes disease. Dissemination occurs via fetal circulation to other organ systems.

Congenital TB should be distinguished from postnatal TB which is acquired during postnatal period due to contact with an active case of TB. Regarding breastfeeding and TB, breast milk is intact of contamination, so transmission of disease does not occur.

CLINICAL MANIFESTATIONS

Clinical manifestations of congenital TB are very non-specific, due to which the diagnosis is challenging. Symptoms include poor feeding, failure to thrive, lethargy, irritability, cough, respiratory distress, fever, vomiting, abdominal distension and seizure. On examination, hepatosplenomegaly and lymphadenopathy are very common. Jaundice due to obstruction by the glands in the porta hepatitis may occur and skin lesions (papular or pustular) may be found in few cases.⁴ Rarely, otitis media with or without mastoiditis is the first sign of congenital TB. Some may present with progressive liver dysfunction without any respiratory symptoms.

INVESTIGATIONS

Mother

Many mothers are asymptomatic, therefore a thorough maternal history and examination regarding tuberculosis during pregnancy is very important. Work up of the mother should be done including a histological examination of placenta at birth, Montoux test, chest X-ray and endometrial aspiration and curettage.

Neonate

Standard workup such as complete blood count, C-reactive protein, erythrocyte sedimentation rate, liver function tests are less efficient when investigating for TB in neonates.

Other investigations

Microscopy and culture

For the detection of Mycobacterium bacilli conventional microscopy (Ziehl-neelsen or Kinyoun stain) or fluorescence microscopy (auramine stain) are used. Samples could be collected in newborns from various sites including gastric aspirates, sputum (induced), tracheal aspirates (if mechanically ventilated), skin lesions, ear discharge, ascitic fluid, cerebrospinal fluid (CSF), and pleural fluid to look for acid fast bacilli and culture. Early morning gastric aspirates to infants with pulmonary illnesses have a 75% positive yield, which is remarkably higher than older children. Liver or lymph node biopsy may be undertaken for histology and culture, but it is highly invasive method for neonates.

Gene Xpert (real time PCR)

Cartridge-based nucleic acid amplification test (CBNAAT) is a Mycobacterium tuberculosis-specific automated, cartridge-based nucleic acid amplification assay, having fully integrated and automated amplification and detection using real-time PCR, providing results within 100 minutes. It is highly specific and extremely helpful in the diagnosis of congenital TB. It also detects rifampicin resistance as it targets the rpoB gene of mycobacteria.

Detection of Mycobacterium tuberculosis bacilli DNA in bronchoalveolar lavage (BAL) by polymerase chain reaction (PCR) is an efficient method, for diagnosis in newborn.⁵

Morphological and histological examination of the placenta in suspected cases at the time of delivery is extremely informative.

Mantoux test

If the mantoux test is positive, it is a supportive evidence for the diagnosis of TB. However, if the tuberculin test is negative it does not rule out TB because neonates have low reactogenicity and poor helper T cell responses. In the classical study of Hageman et al only 2 out of the 14 infants with congenital TB had positive tuberculin tests.

Imaging

Chest radiography and computed tomography (CT) suggests presence of scattered infiltrates, bronchopneumonia, consolidation or periportal

hypodensity. Abdominal ultrasound or CT in order to look for caseating granuloma of liver.

Liquid based mycobacteria growth indicator tube (MGIT) is also used for detection of bacilli. Indirect methods include rapid interferon gamma assays, Quanti FER On-TB Gold assay and T-SPOT using antigens ESAT-6, CFP-10 and TB7, however these tests have shown inconsistent results in neonates.

Phage typing

This has been recently introduced to establish the identity of mycobacteria isolated from mother and the infant.

Once the mother and the neonate are diagnosed with TB, both should undergo screening for Human Immunodeficiency Virus (HIV) because increased incidence of co-infection by both TB and HIV have been documented.

Diagnostic criteria

Diagnostic criteria for the diagnosis of congenital tuberculosis were first described by Beitzki⁶ in 1935 and subsequently these were revised by Cantwell in 1994.⁷

Beitzki criteria

- Isolation of Mycobacterium tuberculosis from the infant.
- Demonstration of primary complex in the liver. In case of absence of primary complex in the liver - evidence of tuberculosis within days after birth.
- Absence of contact with a case of tuberculosis after birth.

Revised criteria by cantwell

Proven tuberculosis lesions in the infant plus one of the following: Lesions occurring in the neonate in the first week of life.

- Primary hepatic complex.
- Identification of Mycobacterium tuberculosis in maternal genital tract or placenta.

Liver biopsy, in order to identify caseating granulomas remains an acceptable alternative to a primary liver complex. Detection of the bacilli in the female genital tract after birth or in placenta was also added to the secondary diagnostic criteria. One important criterion is the exclusion of postnatal acquisition by thoroughly investigating the close contacts. Congenital TB is diagnosed by the primary criteria along with at least one of the secondary criteria.

Limitation to Cantwell criteria

- Presentation may be late; after 2-3 weeks of birth.

- Difficulty in demonstration of AFB in neonates if GA is negative.
- Inadequate opportunities for examination of placenta/endometrium.
- Percutaneous liver biopsies are also difficult to perform, especially in sick neonates with multiple co morbid factors.
- Incomplete evaluation of mother, especially if symptoms of TB are not florid and inadequate evaluation of contacts, including hospital attendants compounds the problem.

Prevention

Revised National TB Control Program (RNTCP) and Indian Academy of Pediatrics (IAP)⁸

Chemoprophylaxis

Preventive therapy is recommended for all neonates whose mother has any form of active TB whether pulmonary or extrapulmonary detected in pregnancy or after birth or if the neonate exposed to any infectious case of TB after birth. Isoniazid prophylaxis should be started after ruling out congenital TB and should be continued for 6 months. RNTCP does not recommend chemoprophylaxis in MDR contacts since the efficacy of 2nd line drugs in preventing TB is not unequivocally established and also because these drugs can be fairly toxic.

Isolation and breastfeeding

Separation of the mother and infant is no longer considered mandatory and she can continue breastfeeding, once the mother's anti-tubercular therapy (ATT) has been started and if baby is on prophylaxis. Appropriate cough hygiene and cough etiquette should be observed by the mother. Separation should be considered in some situations such as the mother is very sick and require hospitalization, she is non-adherent to her treatment, and/or she has drug resistant strain of M. tuberculosis.

Vaccination

BCG reduces the risk of tuberculosis in exposed infants, and hence all children born to mother with TB should receive BCG at birth even if they are on isoniazid preventive therapy.

World Health Organization (WHO)⁹

Chemoprophylaxis

Assess the neonate, if the newborn is clinically unwell then consider TB disease. Isoniazid prophylaxis is started only after the TB disease has been ruled out. Isoniazid

prophylaxis is continued for 6 months. After that, if Mantoux negative, isoniazid is stopped.

Isolation and breastfeeding

Isolation is recommended only in cases of MDR TB. Mother should breastfeed the baby, but infection control measures should be taken to prevent transmission of infection from mother to baby.

Vaccination

Delay BCG until isoniazid prophylaxis is completed. BCG should be administered after 2 weeks of completing the prophylaxis.

American Academy of Pediatrics (AAP)¹⁰

Chemoprophylaxis

Preventive therapy is recommended for all neonates whose mother has any form of active TB in pregnancy or after birth or if the neonate exposed to any infectious case of TB after birth. Isoniazid prophylaxis should be started after ruling out congenital TB and should be continued for 3-4 months followed by Mantoux test. If Mantoux negative stop isoniazid by 3 months. If Mantoux is positive, infant should be investigated for TB. If infant is diagnosed with TB then treatment is started, else isoniazid is continued for 9 months.

Isolation and breastfeeding

If the mother is on ATT, separation is not advised and mother can continue breastfeeding the baby. However, cough hygiene and cough etiquette should be observed by the mother. Separation is advised only in cases of MDR-TB, mother non-compliant to therapy, and/or before starting ATT in mothers who has contagious TB.

Vaccination

BCG should be administered if mother has MDRTB or is poorly adherent to the treatment.

Treatment

No therapeutic trials have been conducted for the treatment of congenital TB. Therefore, no tangible guidelines have been advised. However, congenital TB is always fatal if untreated. Therefore, treatment of the neonate should be initiated as soon as the diagnosis is suspected without waiting for laboratory confirmation, however appropriate specimens should be obtained fast for bacteriological and histological examination.

Testing for drug susceptibility is crucial for both the mother and the neonate, particularly given the existence of multidrug-resistant tuberculosis (MDR TB). Awaiting the results of drug susceptibility, neonates suffering from

pulmonary and extrapulmonary disease should undergo a regimen of four drugs like older children and adults with active disease until sensitivity is known.

There are two types of treatment of tuberculosis:

- First-line treatment: isoniazid, rifampicin, pyrazinamide, and ethambutol.
- Second-line treatment include aminoglycosides, fluoroquinolones, capreomycin, ethionamide, cycloserine, and para-aminosalicylic acid.

Drug treatment should be given for 6 months: isoniazid (H), rifampicin (R), pyrazinamide (Z) and streptomycin (S) for 2 months and HRE for 4 months. AAP recommend isoniazid, rifampicin, pyrazinamide, streptomycin, kanamycin for 9-12 months. Table 1 shows the dosage of first line anti-tubercular drugs.

Table 1: Drug dosage of first line anti-tubercular drugs.

Drug	Range	Average
Isoniazid (H)	7-15mg/kg/day	10mg/kg/day
Rifampicin (R)	10-20mg/kg/day	15mg/kg/day
Pyrazinamide (Z)	30-40mg/kg/day	35mg/kg/day
Ethambutol (E)	15-25mg/kg/day	20mg/kg/day
Streptomycin (S)	15-20mg/kg/day	20mg/kg/day

Corticosteroids in tubercular meningitis, pericarditis, miliary TB with alveolo-capillary block and uveitis. Steroid may be used in endobronchial tuberculosis, bronchial compression, mediastinal compression syndrome, pleurisy with severe distress, laryngeal TB, and TB IRIS. Prednisolone 1-2mg/kg/day or dexamethasone 0.6mg/kg/day or its equivalent is given for 4 weeks and then tapered over the next 4 weeks. Any steroid in equipotent doses can be used.

Monitoring and follow up

Infants should be monitored while on treatment to look for drug response or any worsening, however no details regarding the timing or the modes of monitoring exist. AAP recommends that infants receiving prophylaxis should have clinical surveillance.

RNTCP suggests follow up for pediatric population: Clinical and Laboratory.

Clinical follow up

Should be done every month during treatment. After completion of treatment it may be every 6 months for 2 years. An Initial visit within 2 weeks of starting therapy to re-check that patient is on correct dose and combination and is tolerating all drugs is desirable, where possible. On each follow up child should be assessed for improvement in clinical symptoms. Most patients will

show amelioration of symptoms by the end of 4 weeks of therapy.

Relevant examination should be done including respiratory rate, heart rate, temperature, chest indrawing, lymph node size, organomegaly or abdominal distention, chest examination for breath sound, crepitations, examination of cardiovascular system if pericardial TB, examination of central nervous system if CNS TB was diagnosis.

Weight of the child should be recorded to nearest 0.1 Kg by using appropriate weighing scale (Bassinet type electronic weighing scale for infants) and check for weight gain in comparison to weight on the last visit. If child is losing weight or assessed to be unresponsive to treatment, he should be reevaluated for TB/drug resistant TB or alternative diagnosis by seeking expert advice. Adherence to the therapy is assessed at each visit. Pill count, social support, family-based DOT and treatment supervisor should be used as needed.

Monitoring by laboratory investigations

DOTS recommend chest X-ray at the end of treatment or earlier if clinically there is no improvement or any complication or deterioration. Liver function tests if hepatotoxicity is considered or developed.

Prognosis

The prognosis is poor if treatment is not given. On chemotherapy, the overall survival rate has improved. Delay in the diagnosis of congenital TB contributes to the increased mortality.

DISCUSSION

As the burden of tuberculosis is increasing all over the globe, incidence of congenital TB is also likely to increase. Congenital TB can be transmitted trans placentally, where primary complex is in liver; aspiration of infected amniotic fluid during birth, when lungs are primary focus; and ingestion of infected material, where the primary is in the gut.⁷ Diagnostic criteria were first established by Beitzke in 1935, and later modified by Cantwell.^{6,7} Signs and symptoms are usually non-specific and are often confused with other condition like sepsis and congenital infection. Congenital TB has a very high mortality rate, and those presenting before 4 weeks have mortality up to 50%.² Moreover, most of the mothers are asymptomatic. Therefore, screening of mothers for tuberculosis should become mandatory, which would help in early diagnosis of the disease in the neonate and

prompt treatment. Eventually this would help in minimizing the morbidity and mortality due to congenital tuberculosis.

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